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PARP Inhibition: A Method of Treating and Preventing Certain Cancers

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Abstract

Breast cancer is one of the largest causes of cancer related deaths in women. Less than 5% of breast cancer cases are genetically inherited and most often develop after menopause. The BRCA gene mutation is a genetic inheritance which increases one's chances of developing breast cancer at a young age tenfold. Recent research has proposed a method of treatment in genetically inherited breast cancers by taking advantage of the impaired DNA repair pathway caused by the BRCA mutation. The combination of a BRCA mutation, which leads to deficient double strand DNA repair, and PARP inhibition, which leads to deficient single strand DNA repair, has proven to be synthetically lethal to tumor cells. Clinical trials are determining if this method should be used as a mono-treatment or as an enhancer to other treatment options. Research has also shown that PARP inhibition may be extended to non-genetic cancers as well by targeting similar proteins involved in DNA repair and cell cycle regulation. The most effective inhibitors, their dosages, and side effects are still being studied in clinical trials. The purpose of this paper is to determine the most effective way to take advantage of the synthetically lethal relationship between PARP inhibition and DNA damage repair deficiencies.

Introduction

Damage to DNA happens on a regular basis due to normal metabolism mishaps and external triggers. DNA breaks are categorized into two types: double strand and single strand. The healthy body has DNA repair pathways in place to repair both kinds of breaks. Both the Homologous Recombination pathway and the Non-homologous End Joining repair pathway work to repair double strand breaks. The Base Excision repair pathway repairs single strand breaks. As long as there is damaged DNA in a cell, the cycle should be stopped, preventing the cell from dividing. If the damage cannot be repaired, the cell has systems in place to initiate apoptosis. This paper explores the possibility of taking advantage of the systems in place to initiate apoptosis as a method of killing out tumorous cells.

Methods

The Touro database and PubMed.gov were used to find articles and original research regarding PARP inhibition in genetic cancers as well as cancers resulting from Homologous Recombination deficiencies. Articles referenced in the articles found on the above mentioned databases were used as well.

Double Strand Break Repair Pathways

Although both the Homologous Recombination (HR) and Non-homologous End Joining (NHEJ) repair pathways work to repair double strand breaks, the HR repair pathway is a much more reliable pathway. The HR pathway uses a sister chromatid as a template to repair the damage, which allows the repair to be extremely precise. Because sister chromatids are only available in the S and G2 phases of the cell cycle, HR occurs at those points in the cycle. NHEJ is a less complex process which does not require a template; the two broken ends are joined by ligation, a less precise process which often results in insertion or deletion of nucleotides (Murphy, 2010). (Figure 1)

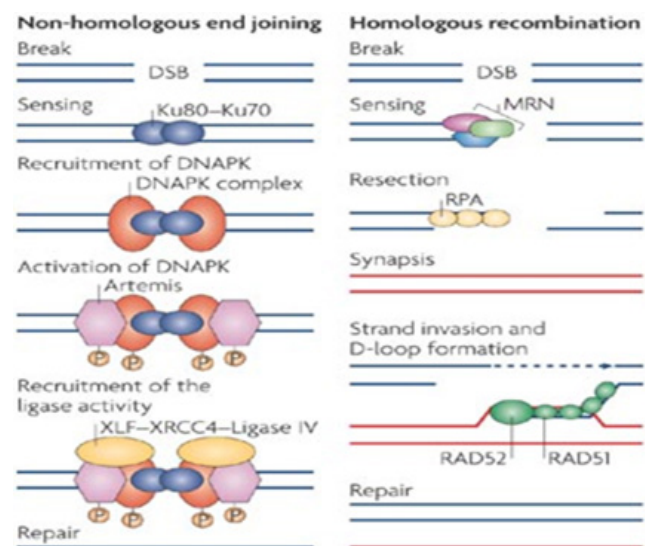


Figure 1

Homologous recombination repair: A DNA lesion is recognized by the MRN (MRE11-RAD50-NBS1) complex, which is recruited to the DSB to generate single-stranded DNA by resection (see the figure; right panel). The single-stranded ends are bound by replication protein A (RPA), RAD51 and RAD52 and can subsequently invade the homologous template, creating a D-loop and a Holliday junction, to prime DNA synthesis and to copy and ultimately restore genetic information that was disrupted by the DSB.
HR: Homologous Recombination, NHEJ: Non-homologous End Joining

The BRCA Gene: A Tumor Suppressor

The BRCA gene functions as a tumor suppressor gene, a category of genes which repress the cell cycle and promote apoptosis. Tumor suppressor genes are in place to prevent damaged DNA

from replicating and integrating into the genome. The most established role of the BRCA gene is its regulation of the Homologous Repair pathway. Cells with mutations in the BRCA gene thus lead the cell along the more error prone NHEJ pathway, causing an accumulation of chromosomal abnormalities and instability, which contributes to tumorigenesis. Mutations in the BRCA gene have been shown to cause a significant increase in the probability of developing tumors of the breast and ovaries. Breast cancer resulting from a BRCA mutation, however, is unique in the sense that only the tumor cells are deficient in the HR repair pathway. Healthy cells have fully responsive repair pathways. This allows treatment targeting this deficiency to be specific only to tumor cells (Murphy, 2010).

The Role of the PARP Enzyme in Single Strand Repair

The PARP enzymes' main function is to initiate the Base Excision Repair pathway by recruiting specific proteins to the site of single strand DNA breaks; once the proteins are recruited, the PARPs are released and the resultant protein complex does the actual repair work. After initially binding to the DNA using its zinc finger domains, the PARP begins to transfer ADP ribose units from NAD⁺ to a variety of acceptor proteins, thus creating a negative charge which recruits the enzymes necessary for base excision

repair (Drew, Calvert, 2008). PARP inhibitors work either by trapping the PARP on the DNA, preventing the protein complex from beginning its repair work, or by actually inhibiting the enzymatic activity. Without PARP to initiate the Base Excision Repair process, the single strand breaks accumulate and eventually develop into double strand breaks. (Figure 2)

Inhibition of the PARP Enzyme in BRCA Deficient cells is Synthetically Lethal

Inhibition of PARP causes an increase in DNA single strand breaks, which eventually evolve into double strand breaks at the site of the original damage. Cells with a functional BRCA network can respond to the inhibition of PARP through the use of the double strand repair pathways. Cells with deficient BRCA genes, however, are unable to properly respond to inhibition of PARP, leaving the double strand breaks without a reliable repair method, causing the two deficiencies to become a synthetically lethal combination (Warrener, et al., 2012). Synthetic lethality is a condition by which deletion or inactivation of only one of two genes would not cause cell death, but deletion or inactivation of both of them is lethal (Reinbolt, 2013). Thus, the inhibition of PARP in healthy cells is not necessarily lethal because the double strand break repair pathways can kick in to repair the damage. When paired with homologous repair deficiencies, however, the inhibition of PARP has proven to

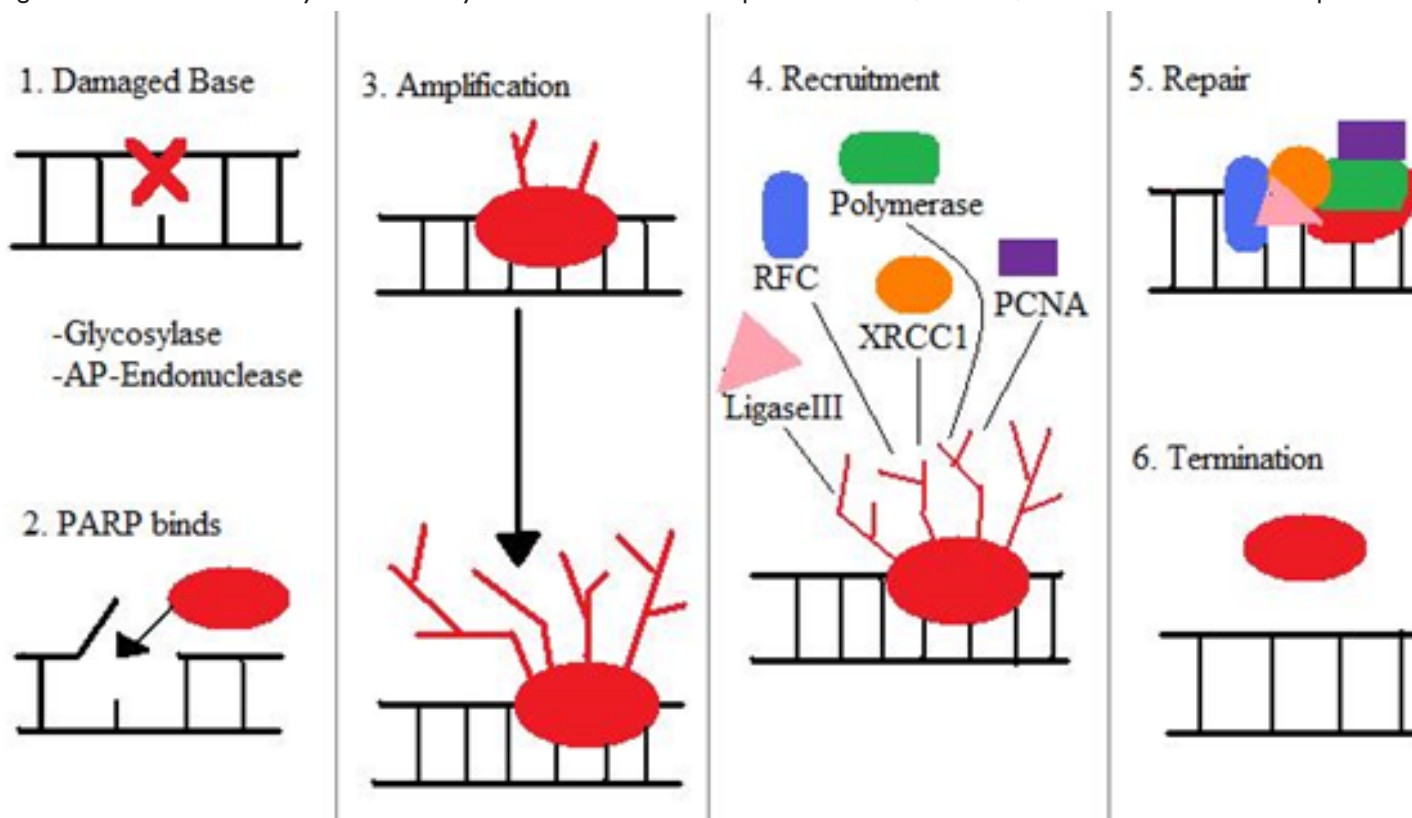


Figure 2:
PARP: Poly-ADP Ribose Polymerase

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be lethal, because there are no efficient repair pathways for single or double strand damage. With no repair pathways in place, the cell is unable to maintain a stable cell cycle and should eventually undergo apoptosis. Inhibition of the PARP enzyme in tumor cells resulting from homologous repair deficiencies inhibits single strand repair mechanisms, initiating a selectively lethal response in the tumor cells, allowing for effective and targeted treatment.

Proteins Involved in the HR Pathway

Homologous recombination is a pathway which involves many different proteins. Identifying the roles these proteins play is a possible way of determining a biomarker to predict if tumor cells will respond to PARP inhibition. RAD51 is a protein which has been found to co-localize with BRCA2, which is suggestive of the interconnected roles they each play in homologous recombination. The HR pathway is initiated in either the S or G2 phases of the cell cycle by a double strand break. The broken ends then need to be resected to expose 3' single stranded DNA tails, which need to be loaded with RAD51 in order to invade the identical homologous strand of the sister chromatid and form new identical DNA (Golmard, et al., 2013). BRCA2 has been shown to have binding sites for both DNA and RAD51 and thus facilitates the localization and binding of RAD51 to the single strand DNA. Without the aid of BRCA2, the RAD51 is unable to bind to the DNA and the HR repair is unable to proceed (Murphy, 2010). BRCA1 is also involved in initiating double strand repair by playing an active role in resecting the broken DNA.

Cyclin-dependent kinases serve as regulators of the HR pathway

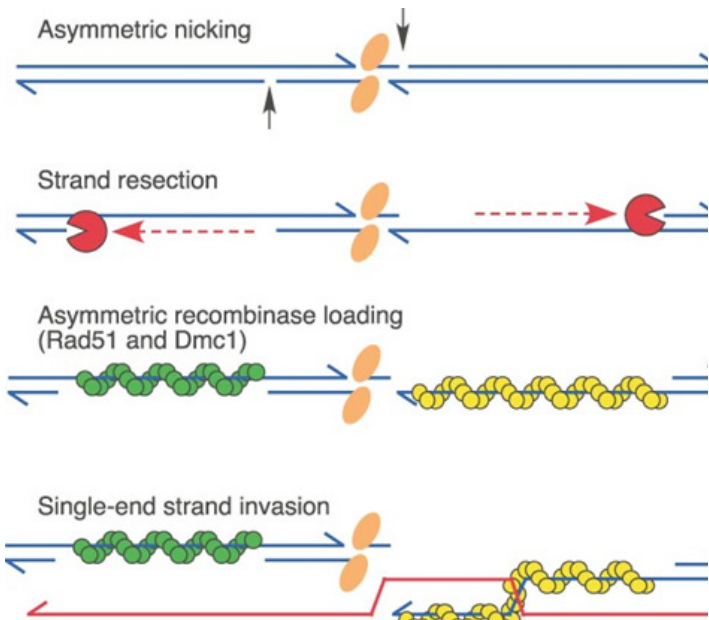


Figure 4: (Google Images)

through their roles in phosphorylation. They can phosphorylate BRCA2 at the RAD51 binding domain and thereby block the binding of DNA and RAD51. This decreases the rate of HR, and is meant to occur when the cell is exiting the G2 phase of the cycle, and HR can no longer occur. They also phosphorylate the protein CtIP, causing it to bind to a BRCA1 domain, which then becomes activated and is responsible for the resection of the broken strand of DNA to expose a 3' tail, initiating the entire HR pathway. Cells

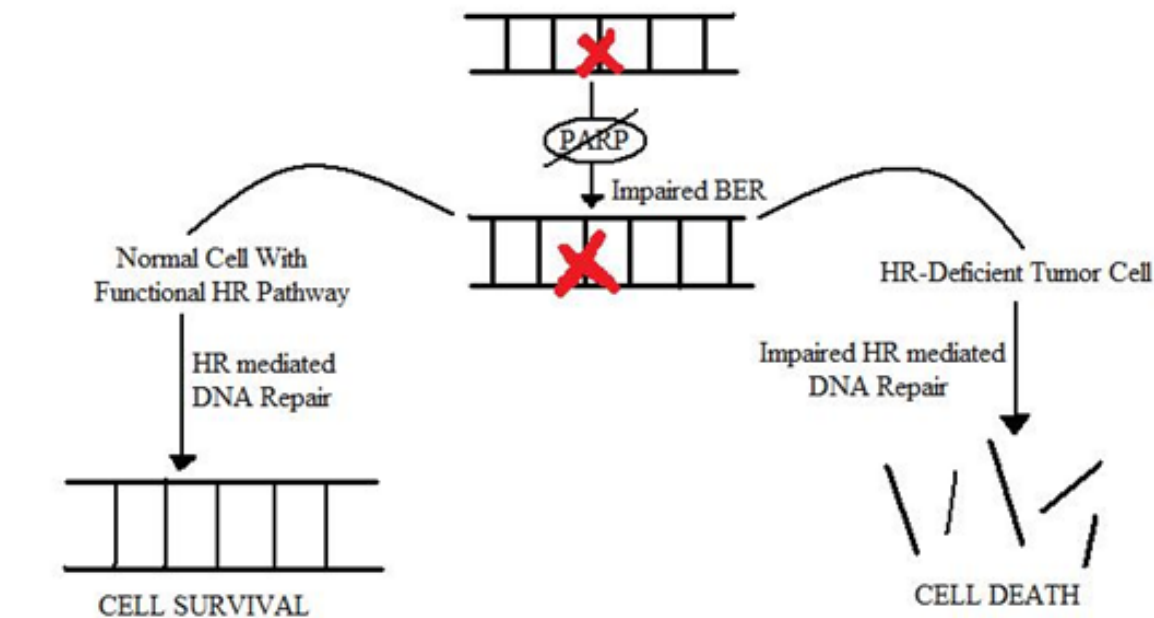


Figure 3: HR: Homologous Repair, BER: Base Excision Repair

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without CtIP have been shown to have defects in the HR pathway, which is indicative of the involved role it plays in Homologous Recombination (Murphy, 2010).

ATM is a kinase involved in phosphorylating many proteins involved in DNA repair and cell cycle check points. Cell cycle checkpoints are in place to ensure that there is no damaged DNA before the cell moves into the next phase. (Dujka, et al., 2010) Studies have been done to determine if lack of ATM induces sensitivity to PARP inhibition, due to the lack of yet another DNA repair mechanism. ATM was genetically repressed in breast cancer cells which were then treated with Olaparib, a PARP inhibitor. The results were compared with a control group of breast cancer cells with active ATM. The control group cells got stuck at the G2/M checkpoint, but only the ATM depleted cells actually initiated apoptosis (Mantani, et al., 2013). These results indicate that ATM deficiency is not necessary for response to PARP inhibition but it does enhance the overall response greatly. Deactivating ATM in a cell is a possible way of increasing the response it will have to PARP inhibition.

P53 is a tumor suppressor protein which is activated in response to DNA damage. P53 is normally held inactive by the mdm2 complex, which it is bound to. In response to DNA damage, p53 dissociates from mdm2, and binds to the damaged DNA (Clegg, et al., 2012). Once activated, p53 activates p21, which then inhibits CDK2, a complex important in transitioning in the cell cycle (Zhao, et al., 2012). The cell cycle is then stopped, giving time for the proper repair proteins to be recruited to repair the damage. If the damage is repaired, then p53 is deactivated and the cell cycle continues. If the damage cannot be repaired, p53 initiates apoptosis. It has been found that p53 is somewhat regulated by the BRCA gene, implying that a mutation in BRCA will cause a similar deficiency in p53 (Murphy, 2010). This correlation explains why BRCA mutated cells are prone to becoming tumorous; the tumor suppression system regulated by p53 is not fully responsive, and is unable to properly respond to the unrepaired DNA damage.

Proteins as a Biomarker to Determine Sensitivity to PARP Inhibition

Identifying if cells are deficient in proteins involved in HR, such as RAD51, CtIP, ATM, CDK's and P53 can be a method of determining if a tumorous cell will respond to PARP inhibition. In addition, inducing mutations in these proteins and other proteins involved in DNA repair can be a way to prompt sensitivity to PARP inhibition, even in cells that are not necessarily deficient in BRCA (Reinbolt, 2013).

Discussions

Trial experiments have been done to study the most effective way to take advantage of the synthetically lethal relationship between

PARP inhibition and BRCA gene mutations. Different inhibitors have been identified and tested in varying doses. Various side effects have been identified, and the timing of the therapy has been experimented with. It is questionable whether to use PARP inhibition as a single agent or as an enhancing agent to other treatment options.

PARP inhibition has been shown to enhance the effects of DNA damaging agents, such as ionizing radiation and chemotherapy. The principle driving the success of radiation therapy, for example, is that oxidizing free radicals are induced to produce single and double strand breaks, prompting the tumorous cells to initiate apoptosis. (Abolfath, 2013) The role PARP plays in repairing DNA damage is a potential resistance mechanism to the desired effect of the radiation. Thus inhibition of the PARP enzymes is not only allowing the radiation to produce the desired results, but it enhances the effects by creating even more breaks (Basu, et al., 2012).

Zinc deficiency and arsenic as potential PARP inhibitors

The zinc finger domains on PARP are what allow it to bind to DNA, beginning the whole Base Excision Repair process. Without being bound to DNA, PARP is essentially useless. Thus a deficiency in zinc ultimately leads to PARP inhibition due to the resultant inability of the PARP to bind to DNA. Research has also shown that arsenic can bind to the zinc finger domain in place of zinc, which changes the zinc finger structure, also preventing it from binding to DNA and causing it to lose all functionality (Sun, et al., 2014). Practically, zinc levels can play a dual role: they are a possible biomarker to determine cell sensitivity to PARP inhibition and depletion of the metal is a method of inducing the inhibition. Arsenic, as well, although via a different mechanism than the others, is considered to be a PARP inhibitor.

Olaparib as a monotherapy in BRCA1/2 mutation associated breast cancers

In a study done in 2008, Olaparib, a PARP inhibitor taken orally, was administered to a group of women all possessing mutations in BRCA1 or BRCA2 genes. Olaparib was taken as a monotherapy, but all the patients had been given at least one chemotherapy regimen earlier. The study had 2 cohorts, the first was 400 mg of Olaparib, which was established to be the maximum tolerable dose, taken twice daily. The second was 100 mg of Olaparib, also taken twice daily. Both study schedules lasted for 168 days. In the first cohort, 41% of the patients achieved the objective response, with 4% achieving a complete response and 37% achieving a partial response. Forty four percent still had stable disease and 15% had progressive disease. The second cohort had only 22% who achieved the objective response, with no patients achieving a

complete response. Forty four percent still had stable disease and 33% had progressive disease (Tutt, et al., 2010). The results of this trial show definite response of tumor cells to Olaparib. The higher dosage produced better results compared to the lower dosage, implying an enhanced response when the dosage is raised.

Olaparib in combination with Paclitaxel

Triple negative breast cancer, TNBC, is defined by lack of receptors for estrogen, progesterone, and human epithelial growth factor; and responds to few treatment options. TNBC has been shown to share similarities with BRCA1 associated breast cancers, (Nowsheen, et al., 2012) and a study was done in TNBC patients to determine the effect of combining PARP inhibition with Paclitaxel, a chemotherapy agent which stabilizes microtubules. The combined effect should prevent them from breaking down during cell division, causing the cell cycle to be stopped and apoptosis to be initiated. Patients received 200 mg of Olaparib twice daily and 90 mg of paclitaxel once a week for 6-10 28 day cycles. There was a greater than expected occurrence of neutropenia, a decrease in neutrophils which are responsible for destroying bacteria, within the first two cycles, a side effect also found in other studies done testing the combination of PARP inhibition with chemotherapy agents. Neutropenia is common side effect of Paclitaxel, but its occurrence increased significantly when combined with PARP inhibition. At the point which patients were experiencing neutropenia of grade 2 or higher, PARP inhibition was maintained, Paclitaxel administration was stopped and G-CSF was administered until the absolute neutrophil count (ANC) went up. If the absolute neutrophil count went up, Paclitaxel was continued, if it did not paclitaxel was discontinued. Although the rate of neutropenia occurrence increased, up to 40% of patients in the study showed partial response to the combined treatment, a greater response than has been seen with either treatment on its own (Dent, et al., 2013). Research is being done to understand the molecular reasoning of the increased neutropenia occurrence. Studies are also determining the best treatment schedule to minimize the side effects and maximize results.

Niraparib as a monotherapy in BRCA mutation carriers and sporadic cancers

Niraparib is also an oral PARP inhibitor and it has been studied as a monotherapy not only in carriers of the BRCA mutation carriers, but in patients with sporadic high grade serous ovarian cancer as well, which has a high prevalence of Homologous Recombination dysfunction. The study experimented with escalating doses to determine the maximum tolerable dose, which was found to be 300 mg, taken twice daily. Thrombocytopenia and neutropenia presented as side effects but were easily controlled with dose reductions. Results of this study showed that greater response was seen in cells sensitive to platinum, a common base in chemotherapy agents, as opposed to platinum resistant cells. There was

some response seen in platinum resistant cells, however, implying that the resistance mechanisms for PARP inhibition and platinum do not entirely overlap (Sandhu, et al., 2013).

The results of the above studies demonstrate the existence of a relationship between DNA damaging agents, such as chemotherapy, and PARP inhibition. They also establish that PARP inhibition is not only effective in genetic tumors, but in other cancers involving homologous repair deficiencies. The relationship between PARP inhibition and platinum is logical, as they share a common goal of inducing DNA damage. The mechanisms of action, however, are clearly not the same because even the platinum resistant cells showed a response to PARP inhibition. Further understanding of the differences between the two and their resistance mechanisms must be understood in order to maximize the positive effect PARP inhibition can have on platinum resistant tumors. The response shown by the sporadic tumor cells shows promise in expanding PARP inhibition to include not only genetic cancers, but other cancers resulting from HR deficiencies. The key will be in finding a biomarker to determine which cells will respond positively.

Interferon Gamma as an enhancer of PARP inhibition

Because of the role they play in tumor suppression and cell cycle regulation, a study was done to determine if the interferon pathway is affected by or involved in the synthetically lethal combination of PARP inhibition and BRCA gene mutations. The interferon pathway is a crucial response of the immune system to viruses, bacteria, and tumor cells. Interferons are proteins which have various functions, including regulation of the cell cycle, anti-viral responses, and apoptosis. Studies have suggested that interferons serve as regulators of the P53 gene, which is involved in the initiation of apoptosis (Takaoka, et al., 2003). H2AX is a gene which codes for the histone H2A, around which DNA gets wrapped, allowing for organized nucleosome formation. ATM is involved in the phosphorylation of H2A as a reaction to DNA double strand breaks in order to create space for the recruitment of repair proteins. Some of the interferons involved in cell cycle regulation and apoptosis are activated via an ATM dependent pathway, suggesting that an interconnected relationship exists between ATM, H2A, interferons, P53, and PARP (Warrener, et al., 2012).

The above-mentioned study took BRCA silenced cells and studied the effect of PARP inhibition on interferon pathway activation. The PARP inhibited cells showed a three-fold increase in H2A phosphorylation, which is indicative of the increase in double strand breaks which results from the unrepaired single strand breaks. Enhanced activation of the interferon pathway was shown to correspond with the level of response to PARP inhibition, suggesting that the role the pathway plays in promoting apoptosis serves as an enhancer to the effects of PARP inhibition. The study

also determined that when interferon gamma was administered together with the PARP inhibitors, the lethal response increased ten-fold, verifying the involvement of the interferon pathway in initiating apoptosis in PARP inhibited BRCA deficient cells (Warrener, et al., 2012).

Because of the role it plays in initiating double strand break repair, ATM depletion is another possible enhancer of PARP inhibition. When ATM is not active, H2A cannot be phosphorylated, which slows the response of the double strand break repair proteins. A decreased double strand repair response leads to more unrepaired double strand breaks with no method of repairing themselves, thus increasing the amount of cells with sensitivity to PARP inhibition. This relationship was proven in a study which showed increased activation of the interferon pathway in ATM deficient cells, confirming both the dependency of successful PARP inhibition on lack of proper double strand repair mechanisms and the involvement of the interferon pathway in the apoptosis of PARP inhibited BRCA deficient cells (Warrener, et al., 2012).

Possible Resistance Mechanisms to PARP Inhibition

BRCA2 mutated cells have been found to develop resistance to platinum based chemotherapy due to the development of a secondary mutation which corrects the original mutation, restoring BRCA function (Wiedemeyer, et al., 2014). Cells harboring this resistance will also display resistance to PARP inhibition, whose success is dependent on a defective Homologous Recombination deficiency. Not all platinum resistant tumor cells, however, develop as a result of the secondary mutation; those cells are still expected to retain sensitivity to PARP inhibition (Weil, Chen, 2011).

P-gp, P-glycoprotein, is a protein of the cell membrane coded for by the ABCB1 gene that acts as a pump, pumping out foreign substances. This protein is involved in developing drug resistance, and has been shown to be the cause of resistance to some anti-cancer drugs. Up-regulation of the ABCB1 gene has been proven to demonstrate resistance to PARP inhibition due to the increased presence of P-gp. This resistance, however, has been counteracted with the administration of Tariquidar, a P-glycoprotein inhibitor (Weil, Chen, 2011).

53BP1 is a protein attached to DNA which is replaced by BRCA1 during DNA damage repair. If 53BP1 is not replaced by BRCA1, the HR pathway becomes inhibited. If 53BP1 is absent in a cell, even in the case of a BRCA mutation, HR is still able to proceed because there is no 53BP1 which needs to be displaced. Only when 53BP1 is present and there is a BRCA mutation is HR actually impaired. An absence of 53BP1, therefore, is a possible resistance mechanism to PARP inhibition, through its restoration of the HR pathway (Weil, Chen, 2011).

PARP inhibition as a proactive treatment option

Until recently, BRCA1/BRCA2 mutation carriers have been faced with the disheartening knowledge that they will most likely develop breast or ovarian cancer and the only proven preventative measure to be taken was prophylactic surgery. The evolution of PARP inhibition as a treatment option also introduces the possibility of using PARP inhibition as a chemo-preventative measure for BRCA carriers who did not yet develop cancer; a much less drastic measure than prophylactic surgery. There have not been any conclusive studies done regarding using PARP inhibition as a preventative treatment, but the same mechanism it uses to selectively kill tumor cells has been proposed as a way of preventing them from developing in the first place. Tumor cells resulting from BRCA deficiencies are the result of genetic alterations and defective DNA repair. Pre-exposing a BRCA mutation carrier to PARP inhibitors is a proposed method of killing the genetically altered cells, preventing them from developing into full blown tumors. It has also been proposed to use PARP inhibition as a means of preventing relapse, but no conclusive studies have been done at this point to investigate the possibility of success in this approach. Eventualities which must be considered in using PARP inhibition as a long term treatment option are the side effects as well as the danger in maintaining a defective repair pathway long term, especially in already high risk patients (Vinayek, Ford, 2010).

Conclusions

PARP inhibition shows promise on many different levels. The main factors to bear in mind in the development of treatment options are the specific target of only tumorous cells and minimal side effects, both of which are realized in PARP inhibition. The success of PARP inhibition expanded from genetically inherited breast cancers to other cancers resulting from DNA damage repair defects was demonstrated in clinical trials, which expands the network of patients eligible for treatment, making it easier to maintain the funding of research. PARP inhibition has elicited positive responses both as a mono-therapy and as an enhancer of other DNA damaging agents, such as chemotherapy and radiation. The proteins involved in Homologous Recombination show great promise in functioning as predictive biomarkers of sensitivity to PARP inhibition. Further understanding of the roles they play will enable mutations of those proteins to be a method of inducing and/or enhancing sensitivity to PARP inhibition. The hope that PARP inhibition presents not only as a treatment option but also as a precautionary alternative to prophylactic surgery makes the investment needed to make it a reality most worthwhile.

Abbreviations

PARP	Poly ADP-ribose polymerase
HR	Homologous Recombination
NHEJ	Non-homologous End Joining
BER	Base Excision Repair
ATM	Ataxia Telangiectasia Mutated

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